89

Guidance for Industry

ENVIRONMENTAL IMPACT ASSESSMENTS (EIAs) for VETERINARY MEDICINAL PRODUCTS (VMPs) - PHASE I

VICH GL6

DRAFT GUIDANCE

This draft guidance is intended to assist in developing harmonized guidance for conducting environmental assessments for veterinary medicinal products in the European Union, Japan, and the United States.

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Comments and suggestions regarding this document should be sent to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the Docket No. 99D-2975.

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ENVIRONMENTAL IMPACT ASSESSMENTS (EIAS) FOR VETERINARY MEDICINAL PRODUCTS (VMPS) - PHASE I

Recommended for Consultation
at Step 4 of the VICH Process
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ENVIRONMENTAL IMPACT ASSESSMENTS (EIAS) FOR VETERINARY MEDICINAL PRODUCTS (VMPS) - PHASE I

Endorsed by the VICH Steering Committee at Step 3 of the VICH Process

22 October 1998

Introduction

In 1996, the VICH Steering Committee (VICH SC) authorized formation of a working group to develop harmonized guidance for conducting environmental impact assessments (EIAs) for veterinary medicinal products (VMPs) in the European Union (EU), Japan (JP) and the United States (US). The mandate of the VICH Ecotoxicity/Environmental Impact Assessment Working Group (VICH Ecotox WG)**,** [1] as set forth by the VICH SC, is as follows:

> *"To elaborate tripartite guidelines on the design of studies and the evaluation of the environmental impact assessment of veterinary medicinal products. It is suggested to follow a tiered approach based on the principle of risk analysis. Categories of products to be covered by the different tiers of the guideline should be specified. Existing or draft guidelines in the EU, Japan, and the US should be taken into account*."

This document presents guidance on how to conduct Phase I EIAs for VMPs other than biological products. Consistent with the mandate, two phases of EIA are recommended. In Phase I, the potential for environmental exposure is assessed based on the intended use of the VMP. It is assumed that VMPs with limited use and limited environmental exposure will have limited environmental effects and thus stop in Phase I. [2] Phase I also identifies VMPs that require a more extensive EIA under Phase II. [3] Certain VMPs that might otherwise stop in Phase I may require additional environmental information targeted to address particular concerns associated with their use.[4] These situations are expected to be the exception rather than the

[1] Current working group members include Ms. Carol Aldridge (EMEA), Dr. Masatoshi Ishimaru (JMAFF), Dr. Shigehiro Iwabuchi (JVPA), Dr. Charles Eirkson (US/FDA/CVM), Dr. Joseph Robinson (AHI) and Dr. Leo Van Leemput (FEDESA).

[2] In the US, reference to a Phase I EIA is equivalent to either a categorical exclusion or an environmental assessment (EA) conducted under the National Environmental Policy Act (NEPA). A VMP that may stop at Phase I is equivalent to a categorical exclusion or an EA which leads to a finding of no significant impact (FONSI) under NEPA.

[3] Phase II represents a second level of environmental analysis that may include testing. In the US, a Phase II EIA is equivalent to an EA with more extensive data than would be required under the US equivalent of a Phase I EIA. A Phase II EIA may lead to a FONSI or an Environmental Impact Statement under NEPA.

[4] In the US, this is equivalent to an extraordinary circumstance under NEPA.

rule. In an effort to harmonize the EIA to the maximum extent possible, it is expected that the EU, US, and JP will rely on this document for guidance on conducting Phase I EIAs for VMPs.

Phase I Guidance

The Phase I EIA for a VMP makes use of the decision tree in Figure 1. To use the Phase I decision tree, the applicant[5] works through the questions until they arrive at a question which allows them to conclude that their product qualifies for a Phase I report. If there is no information on a particular question, the question is ignored and the applicant continues to the next question. If while working through the decision tree, an applicant determines that their VMP did not need an EIA, Question 1 still applies. When an applicant determines that at least one of the Phase I criteria has been met, the applicant should produce a Phase I EIA report discussing the basis for the decision. If the assessment determines that the VMP has limited exposure for more than one reason, each reason may be discussed to strengthen the Phase I EIA report. However, as suggested by the Phase I decision tree, the types of Phase II studies needed will vary based upon the concerns identified in Phase I. In situations where clarification is needed, it is important that the applicant contact the appropriate regulatory authorities.

Question 1: Is the VMP exempt from the need for an EIA by legislation and/or regulation? [6]

This Phase I question takes into account the different statutory and regulatory requirements among the EU, JP, and US. If the answer to Question 1 is yes, the applicant does not need to continue through the Phase I decision tree but should comply with the region's rules regarding submission of required documentation.

Question 2: Is the VMP a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment? [7]

It is assumed that many natural substances are already present in the environment or are rapidly degraded upon entry into the environment, such that environmental exposure is not altered and there are limited environmental effects. VMPs likely to stop at this question include electrolytes, peptides, proteins, vitamins, and other compounds that occur naturally in the environment. In answering this question, the applicant documents that use of the VMP will not alter the concentration or distribution of the substance in the environment**.**

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[5] In the US, the term "applicant" refers to the drug sponsor.

[6] In the US, this includes products that are categorically excluded under NEPA. If a product is not categorically excluded due to an extraordinary circumstance, however, the answer to this question is no – the VMP is not exempt from the need for an EIA.

[7] In the US, these VMPs are usually categorically excluded under NEPA. (21 CFR 25.33(c), 25.33(d)(1), 25.33(d)(2), 25.33(d)(3), 25.33(d)(4), 25.33(d)(5)).

Question 3: Will the VMP be used only in non-food animals?[7]

Generally, non-food animals are not intensively reared. Also, products used in these animals are usually individual treatments. Approval of VMPs for use in non-food animals is likely to be associated with fewer environmental concerns than approval of VMPs in food-producing animals simply because there is less total amount of product used. The definition of non-food animals varies among the three regions.

Question 4: Is the VMP intended for use in a minor species that is reared and treated similarly to a major species for which an EIA already exists?[7]

VMPs intended for use in a minor species may stop in Phase I provided the VMP is already approved for use in a major species, the minor species is reared under similar conditions as the major species, the VMP is administered by the same route and the total dose administered to the minor species is no greater than that used in the major species. In this case, it is assumed that use in the minor species will have limited environmental impact. There are differences regarding what constitutes major versus minor species among the EU, JP, and US.

Question 5: Will the VMP be used to treat a small number of animals in a flock or herd?[7]

This question may exempt VMPs from the need for a further assessment when the product is used to treat an individual or a few animals in a flock or herd. It is assumed that the approval of VMPs captured under this question will produce environmental exposures well below concentrations that impact the environment. Products used to treat clinically mastitic cows, anesthetics used for surgical purposes, ophthalmics, and hormones used as reproductive aids for individual animals may fall within the scope of this question.

Question 6: Is the VMP extensively metabolized in the treated animal?[8]

It is assumed that VMPs that are extensively metabolized in the treated animal do not enter the environment. Demonstration of extensive metabolism may be accomplished through a radiolabeled residue depletion and excretion study. A VMP may be defined as "extensively metabolized" when analysis of excreta shows that no single fraction exceeds 5% of the total excreted radioactivity**.**

Question 7: Is the VMP used to treat aquatic or terrestrial species?

Environmental concerns are different for products used in aquatic versus terrestrial animals. The answer to this question defines the initial route by which the VMP enters the environment. For VMPs intended for treatment of aquatic species, proceed to Questions 8-13. For VMPs intended for treatment of terrestrial species, proceed to Questions 14-17**.**

[8] In the US, information provided to respond to this question must be provided in an EA that includes documentation and mitigations, as appropriate, to support a FONSI.

Aquatic Branch

Question 8: Is entry into the aquatic environment prevented by disposal of the aquatic waste matrix?[8]

Some VMPs used in aquaculture do not enter the environment because the treatment waste is disposed of by incineration or other means. These VMPs have no opportunity to impact the environment. Applicants answering yes to this question should provide documentation on the means of disposal.

Question 9: Are aquatic species reared in a confined facility?[8]

A confined facility is defined as one in which the effluent can be treated and the discharge controlled. This includes facilities such as tanks, lined ponds, and some raceways. VMPs introduced directly into the aquatic environment have a greater potential to contaminate aquatic habitats. This is because the aquaculture facility is contiguous with the aquatic environment, and there is no opportunity for processing or treatment of effluents. Therefore, any VMP used to treat aquatic species, where the product is placed directly into the environment, e.g., net pens, does not stop in Phase I.

Question 10: Is the VMP an ecto- and/or endoparasiticide?

The ecotoxicity database used to develop the quantitative value used in Question 11, included all classes of pharmaceuticals used in human medicine (Reference 1). Very few parasiticides are used in human therapy thus the human database is insufficient to establish a quantitative trigger value for these compounds. The ecotoxicological potential of this class of compounds needs to be assessed by conducting aquatic effects tests in Phase II.

Question 11: Is the environmental introduction concentration ($EIC_{aquatic}$) of the VMP released from aquaculture facilities less than 1 µg/L?[8]

The rationale for selecting 1 µg/L as the $EIC_{aquatic}$ is provided (Reference 1). This value is below the level shown to have adverse effects in ecotoxicity studies using aquatic species. It is assumed that water released from a confined aquaculture facility with a VMP below this concentration will produce limited environmental effects.

The $EIC_{aquatic}$ applies only to VMPs that will be used to treat fish and other aquatic species in confinement where the effluent can be treated and controlled prior to being discharged into the environment. In order to apply this value, it is necessary to estimate the concentration of VMP expected in the effluent from the aquaculture facility. This involves summing the parent drug and all related metabolites excreted by the target species; as well as accounting for VMP in the uneaten feed and VMP released to water. The $EIC_{aquatic}$ calculation may account for current management and engineering practices provided appropriate documentation is supplied by the applicant. The calculated value is compared against the 1 µg/L value. If the calculated $EIC_{aquatic}$ value for the VMP entering the environment is less than 1 µg/L, then the VMP may stop at Phase I.

Question 12: Do data or mitigations exist that alter the $EIC_{aquatic}$?[8]

The concentration of the VMP in the effluent may be decreased by filtration, settlement, dilution, or other mitigations. Other mitigations (both natural degradation and management practices) may reduce the concentration of the VMP in water and hence reduce environmental exposure. As a specific example, the $EIC_{aquatic}$ for an aquaculture facility may be reduced if additional volumes of water are used during treatment. In addition, UV/ozone treatments may be used to reduce the $EIC_{aquatic}$ if the VMP is known to be labile to these treatments. When the applicant demonstrates a mitigation exists, it can be considered in the calculation of the $EIC_{aquatic.}$

Question 13: Is recalculated $EIC_{aquatic}$ less than 1 µg/L?[8]

This recalculated value is then compared against the 1 µg/L value . If the recalculated $EIC_{aquatic}$ value for the VMP entering the environment is less than 1 µg/L, then the VMP may stop at Phase I.

Terrestrial Branch

Question 14: Is entry to the terrestrial environment prevented through disposal of the terrestrial waste matrix?[8]

If the waste matrix into which the VMP is excreted (e.g., bedding in a poultry house) is disposed of such that entry into the environment does not occur, then the VMP has limited opportunity to impact the environment. The applicant should provide documentation that the matrix does not enter the environment. Incineration of the waste matrix containing the VMP is an example of a means of disposal that would permit stopping at this point in Phase I.

Question 15: Are animals reared on pasture?

For intensively-reared animals that are housed or raised in feedlots, excreta is collected in the form of manure and slurries, stored, and then spread onto agricultural land, with or without ploughing. This is in contrast to animals raised on pasture, where excretion is directly into the environment. For animals reared on pasture, there are specific concerns for certain types of products related to their direct entry into the environment.

Question 16: Is the VMP an ecto- and/or endoparasiticide?

Ecto- and endoparasiticides have specific ecotoxicity concerns especially when used in animals reared on pasture. These VMPs are pharmacologically active against organisms that are biologically related to pasture invertebrates. Because protozoa are not biologically related to pasture invertebrates, products used to treat protozoa are not captured in this question. VMPs not stopping at this question in Phase I, should advance to Phase II to address specific areas of concern, e.g., dung fauna.

Question 17: Is the predicted environmental concentration of the VMP in soil (PEC_{soil}) less than 100 µg/Kg?[8]

The rationale for selecting the PEC_{soil} value of 100 µg/Kg is provided (Reference 2). Since this value is below the level shown to have effects in ecotoxicity studies conducted on earthworms,

microbes, and plants, it is assumed that concentrations less than 100 µg/Kg will produce limited environmental effects.

In order to apply this value, it is necessary to estimate the concentration of the VMP in terrestrial ecosystems. An example on how to calculate the PEC_{soil} for VMP is provided (Reference 3). Other approaches for calculating PEC_{soil} should be used if they are more relevant for a particular region. For calculating PEC_{soil}, a total residue concept is adopted. This involves summing the parent drug with all related metabolites excreted by the treated animal. This assumes that 100% of the dose is excreted unless residue depletion data support a value less than 100%. The total residue approach is considered to be conservative in assessing effects in that it combines parent plus metabolites in calculating environmental concentrations, and metabolites generally have less biological activity than the parent compound. Results from degradation studies in manure and soils may be used to refine the estimate of the concentration of the VMP in soil (Reference 3). The calculated PEC_{soil} is compared against the value of 100 µg/Kg. If the PEC_{soil} for the VMP is less than the value, then the EIA for the VMP may stop in Phase I.

Some products used in intensively-reared livestock may also be used in pasture animals. In such cases, the PEC_{soil} calculations may differ. However, even in the pasture setting there is some migration of the VMP into soil. The PEC_{soil} estimate for a VMP excreted onto pasture assumes direct entry into soil with even distribution in the upper 5 cm of soil. This estimate for whole herd/flock treatments is based upon (1) dose/animal based on mg/kg and body-weight of animal; (2) percentage of dose excreted by the treated animals (use 100% if no excretion data are available); (3) stocking density of treated animals (animals/hectare); (4) excreted VMP is distributed in soil to 5 cm; and (5) bulk density of soil. Effectively, this means that for a soil bulk density of 1,500 kg/m^3, the total dose/hectare is distributed in 750,000 Kg of soil.

REFERENCES

1. Center for Drug Evaluation and Research (CDER), US Food and Drug Administration, 1997. Retrospective review of ecotoxicity data submitted in environmental assessments for public display. Docket No. 96N-0057.

2. AHI Environmental Risk Assessment Working Group, 1997, Analysis Of Data And Information To Support A PEC_{soil} Trigger Value For Phase I (A retrospective review of ecotoxicity data from environmental assessments submitted to FDA/CVM to support the approval of veterinary drug products in the United States from 1973-1997).

3. Spaepen, K. R. I., L. J. J. Van Leemput, P. G. Wislocki and C. Verschueren, 1997. A uniform procedure to estimate the predicted environmental concentration of the residues of veterinary medicines in soil. Environmental Toxicology and Chemistry 16: 1977-1982.

Figure 1. Phase I Decision Tree